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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/648,677	08/25/2003	Ashok V. Purandare	QA0259 NP	3788

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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/648,677	PURANDARE, ASHOK V.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/13/05*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,6 and 8-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6 and 8-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The examiner notes that the amended claims have expanded the scope of the core again, by removing the requirement that the A containing ring be a monoazine; thus this ring can now be e.g. non-heterocyclic.

Claims 1, 6, 8-12 are rejected as being drawn to an improper Markush Group. The claims are drawn to multiple inventions for reasons set forth in the above requirement for restriction. This does not constitute an art-recognized genus. The claims are examined only to the extent that they read on the elected invention. Cancellation of the non-elected subject matter will overcome the rejection. This can be done by 1) setting X=Y=N, 2) requiring that exactly one of A, B, D and E is N

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 6, 8-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The new "includes" in the G definition is open-ended, so what else could G be. Suggested is "can be".
2. The value of n as 4 in claim 1, and 2 in claim 2 makes no sense because the variable is no longer in use.

Claims 1-2, 6, 8-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The revised definition for Z raises the issue of new matter. This material is broader than the last claim 5 species, and, as indicated previously, does not fall within the broadest genus. The limitation to 1, 2 propylene is noted, but that species exists only in the context of where R4-R5 form a ring, only when R2 is piperidine, etc. Thus, subject matter where e.g. R4-R5 do not form a ring is not in the original Formula I and is outside the claim 4 species.

Specification

The amendment is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The page 48 labeling of the data as IC50 is deemed new matter. Applicants make a reference to "native cell line" as providing evidence that this is IC(50) rather than Ki. The reasoning for this was not presented and hence is not understood.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claims 1-2, 5-6, 8-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.
The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Because of the broad scope of R10 and R1, plus the scope of R2, billions of compounds are covered. Claim 5 covers 4 species.

(b) Scope of the diseases covered. Five diseases are listed in these claims.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is minimal. The dosage range information presented on page 40, line 11, gives a 5,000,000 fold daily range, essentially worthless. Moreover, it is not specific to any actual disease; it is completely generic.

(4) State of the Prior Art: The compounds are benzylamino- pyridopyrimidines with a particular substitution pattern. So far as the examiner is aware, no benzylamino-pyridopyrimidines have been used for treatment of any such diseases.

(5) Working Examples: There are none to the treatment of any disorder. Indeed, no biological data is presented on any particular compound. The traverse on this point is noted but is unpersuasive. However: a) It does not state what the particular compound or compounds tested was. There is no way of even knowing whether the compound or compounds tested were part of the elected invention b) the original sentence does not say what this number represents, and the revised sentence is considered as new matter. It could be IC (50) value or it could be the K_i value, both conventional measures of binding, but entirely different ways of calculating it c) the sentence does not give actual data, but instead a 20,000 fold range. This is basically meaningless. A compound that binds at 100 μm (if this is IC (50)) is essentially worthless. The examiner also notes that such a test does not establish that the compound is a CCR4 antagonist. It just establishes binding; it could be an agonist for all this test can determine. In this regard, applicants reply that the specification teaches that the compounds are antagonists. This is understood. The examiner's point, however, is that the testing (the CEM essay on ages 45-48) is so limited that it cannot even establish that the compounds are antagonists. The examiner must also note that the switching of "activity measured was 5...." to "activity was measured over an IC50 value range" actually weakens the statement. The former says that 5 is at least a

potential value; the latter does says that the measuring was done in that range, not that any molecule actually showed up in that range.

(6) Skill of those in the art: The skill level in this art is extremely low. The area of CCR4 antagonists is in its infancy. The Barnes, Cytokine & Growth Factor Reviews Volume 14, Issue 6, December 2003, Pages 511-522 reference devotes exactly one sentence to the topic on page 517, and even that only presents the possibility of a type of action, with no reference to actual therapeutic use. The Allen et al, Bioorganic & Medicinal Chemistry Letters Volume 14, Issue 7 , April 2004, Pages 1619-1624 reference presents in its last sentence only the possibility that such compounds might be useful, nothing more. In terms of Psoriasis, see the Krueger, Journal of the American Academy of Dermatology 46(1), Pages 1-23 (2002) reference. This provides an extrensive review of potential new biological agents, yet CCR4 gets only the briefest passing notice (first column of page 11), indicating the the skill level in this art is negligible. In terms of asthma, see the Barnes, Nature Reviews: Drug Discovery 4, 831 (2004) reference. This has extensive discussion of a wide assortment of "New Drugs for Asthma." CCR4 antagonists get only a brief mention in second column of page 837, which only raises it as possible line of research. So far as the examiner is aware, no CCR4 antagonist has been made effective for treatment of asthma. Much the same is true for COPD and Rheumatoid Arthritis. Although dozens of chemokines are involved in the recruitment of inflammatory cells via activation of an assortment of surface receptors, including CCR4, for inflammatory diosorders such as RA and COPD, no CCR4 antagonists have ever been made effective for the treatment of either disorder. Of the very few drugs that have been made to work for rejection of transpanted organs, none operate via CCR4 antagonism; they instead suppress the immune system. It

is clear that as of now, this is a fairly new area of research. Applicants in their previous response point to the background of the invention. However, merely being an area of research interest does not mean that the skill level in the art is sufficient to get the compounds to work without undeue experimentation. None of these references establish that the skill level in the art is sufficiently high to actually get such a compound to work. Applicants now argue that these "arise from the pharmaceuitical industry." Where the papers arise from is not the issue; what matters is what the references actually teach. In this regard, applicants have ignored the specific teaching of the references cited above, in favor of a list of citations on pages 9-10. These have been reviewed, but if applicants wish them to be made of record, applicants must provide a PTO-1449. Applicants have presented no specific discussion of any of these references. Moreover, the examiner does not necessarily see any direct relevance to the issue at hand. For example, the first reference listed, Campbell, makes no mention at all of CCR4 antagonists being used for therapeutic purposes. The last reference, Biedermann, seems to disparage the very approach of these claims, saying, "This implies that targeting one single chemokine receptor may not result in a sufficient blockage of Th cell migration to a certain tissue." Targeting one receptor is what these claims call for. Some references, e.g. Randolph, don't even appear to mention CCR4. Elsewhere, applicants point to ""many significant references", but these are not identified or discussed.

The remarks also state that "to eliminate doubt", the "antagonist" claim language has been added to claims 8-12. However, since the specification already says that all of these compounds are antagonsits, it is not seem that this wording changes the scope of the claims.

(7) The quantity of experimentation needed: Especially because of issues 1), 3), 5, and 6), the experimentation is expected to be extensive.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

With no established method of use, the compounds themselves cannot be deemed enabled either. In this regard, applicants note that the specification gives methods for preparation. Agreed, but the issue here is enablement in terms of how to use, n ot make.

Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

These species do not fall within Formula I for reasons set forth previously. Hence they have no ascribed utility, because the utility is defined in terms of Formula I. In addition, the last claim 5 species has G = 1, 2 propylene, a choice not permitted by Formula I in the specification, and hence such a species does not fall within Formula I for that reason as well.

Specification

The status of the application mentioned on page 42 should be provided.

The amendment filed 7/13/05 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as set forth in the new matter rejection to the claims as noted above, since the same text was added to the specification as well.

Applicant is required to cancel the new matter in the reply to this Office Action.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at

571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark L. Berch
Primary Examiner
Art Unit 1624

8/26/05